SINDROME NEFROTICO CORTICORESISTENTE ESTUDIO GENETICO y TRATAMIENTO

PRESENTACION DE 2 CASOS

Dr. Pablo Bonany
Nefrólogo Infantil
-HNRG (CABA)
-EALM (LA PAMPA)

➢ Paciente 1

-8 meses

-Síndrome nefrótico corticoresistente.

-NO se biopsió

-Se solicita estudio genético molecular para NEPHS 1, NEPHS 2, WT1, LAMB2

➢ Paciente 2

- 5 años

-Síndrome nefrótico corticorresistente

-No se biopsió

-Se solicita Panel genético SN 56 genes.

ESTUDIOS GENETICOS: RESULTADOS

- **Paciente 1**

-Estudio genético molecular para NEPHS 1, NEPHS 2, WT1, LAMB2:

SIN MUTACIONES PATOLOGICAS

➢ Paciente 2

-Panel genético SN.

ESTUDIO SOLICITADO

Análisis de variantes en 56 genes relacionados con síndrome nefrótico corticorresistente: *ACTN4 ANLN APOL1 ARHGAP24 ARHGDIA AVIL CD2AP COL4A3 COL4A4 COL4A5 COL4A6 COQ2 COQ6 COQ8B CRB2 CUBN DGKE DLC1 EMP2 FAT1 INF2 ITGA3 ITGB4 ITSN1 ITSN2 KANK1 KANK2 KANK4 LAMA5 LAMB2 LMX1B MAFB MAGI2 MYH9 MYO1E NEU1 NFKB2 NPHS1 NPHS2 NUP107 NUP205 NUP93 PAX2 PDSS2 PLCE1 PTPRO SCARB2 SMARCAL1 TNS2 TP53RK TRPC6 TTC21B WDR4 WDR73 WT1 XPO5*

-Resultado.

RESULTADOS

VARIANTES

Gen	Exón	Cambio Nucleotídico	Proteína	Efecto	Cigosidad £	Profundidad β
TTC21B	26/29	Chr2(hg19): g.166740365 A>C NM_024753.5:c.3623T>G	p.Ile1208Ser	**Incierto**	0.54	**184X**

-Interpretación Biológica

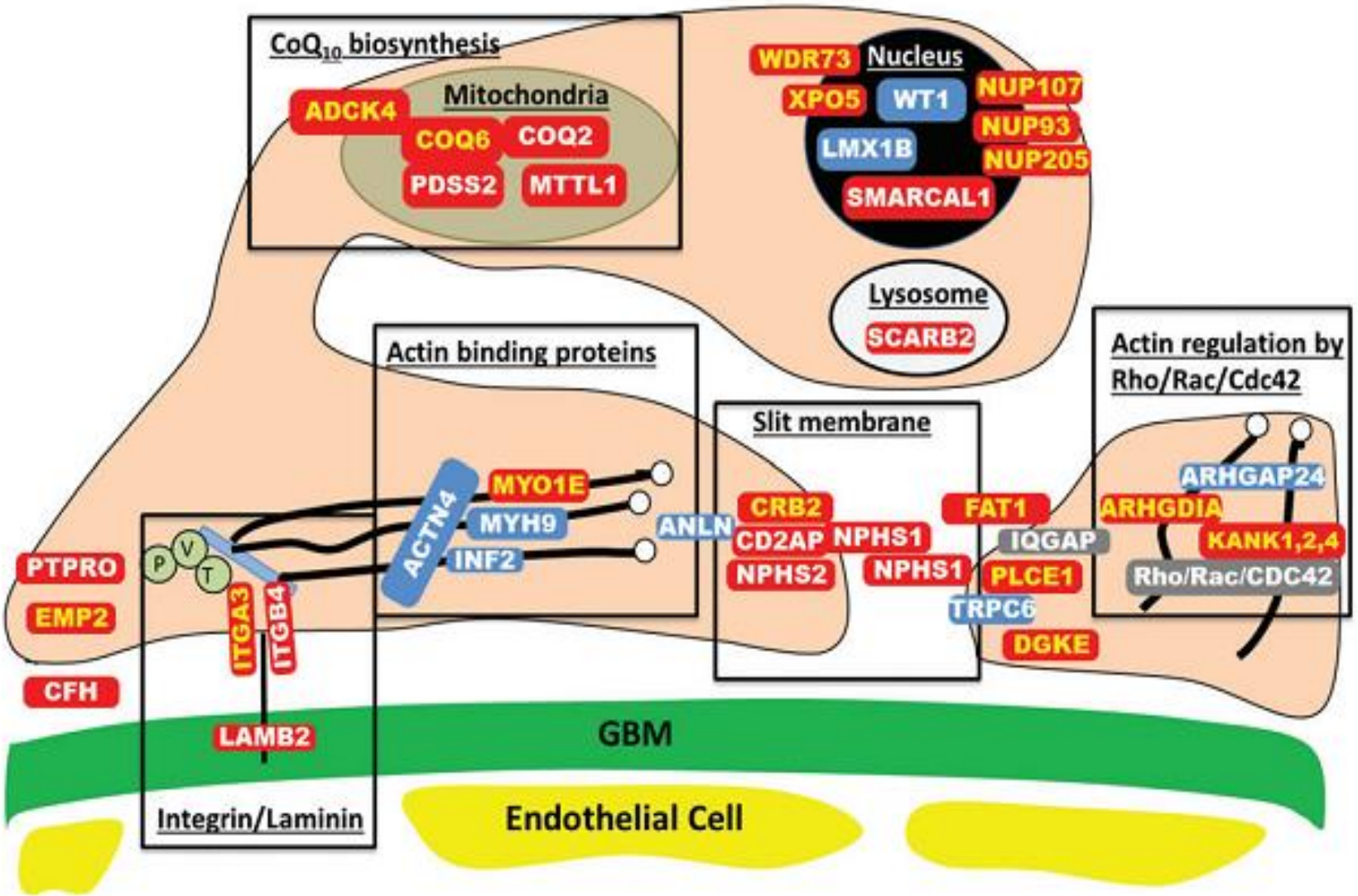
-**Algoritmos de predicción *in silico*** efecto: deletéreo (CADD, DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MutationAssessor, MutationTaster, REVEL, SIFT) y tolerado (BayesDel_addAF, MVP, Polyphen2-HVAR, PrimateAI).

-***TTC21B*** *:* relacionado a Nefronoptisis tipo 12 (MIM 613820)

-**Herencia** autosómica dominante y recesiva.

-**Frecuencia poblacionales** y generales: Muy Baja [C=0.000175(44/251092, GnomAD_exome), C=0.000080 (10/125568, TOPMED), C=0.000223 (27/121264, ExAC), C=0.00003].

-**Clasificación** según ClinVar: **VUS.**


CoQ10 biosynthesis
Mitochondria
ADCK4
COQ6
COQ2
PDSS2
MTTL1
WDR73
Nucleus
XPO5
WT1
NUP107
NUP93
LMX1B
NUP205
SMARCAL1
Lysosome
SCARB2
Actin binding proteins
MYO1E
ACTN4
MYH9
INF2
ANLN
Slit membrane
CRB2
CD2AP
NPHS1
NPHS2
NPHS1
FAT1
IQGAP
PLCE1
TRPC6
DGKE
Actin regulation by Rho/Rac/Cdc42
ARHGAP24
ARHGDIA
KANK1,2,4
Rho/Rac/CDC42
PTPRO
EMP2
CFH
P
V
T
ITGA3
ITGB4
LAMB2
Integrin/Laminin
GBM
Endothelial Cell

¿UN ESTUDIO GENETICO RESTRINGIDO O AMPLIADO A 56 GENES ES SUFICIENTE PARA HACER DIAGNOSTICO?

Genética del SNCR

Table 2. International cohort of 526 of the 1783 families, in whom a single-gene cause of SRNS was detected in 1 of 21 monogenic SRNS genes [49]

Gene causing SRNS	Mode of inheritance	Total SRNS families with molecular diagnosis
NPHS2	AR	177 (9.93)
NPHS1	AR	131 (7.34)
WT1	AD	85 (4.77)
PLCE1	AR	37 (2.17)
LAMB2	AR	20 (1.12)
SMARCAL1	AR	16 (0.89)
INF2	AD	9 (0.5)
TRPC6	AD	9 (0.53)
COQ6	AR	8 (0.45)
ITGA3	AR	5 (0.28)
MYO1E	AR	5 (0.28)
CUBN	AR	5 (0.28)
COQ2	AR	4 (0.22)
LMX1B	AD	4 (0.22)
ADCK4	AR	3 (0.17)
DGKE	AR	2 (0.11)
PDSS2	AR	2 (0.11)
ARHGAP24	AD	1 (0.06)
ARHGDIA	AR	1 (0.06)
CFH	AR	1 (0.06)
ITGB4	AR	1 (0.06)
Total		526 (29.5)

AR, autosomal recessive; AD, autosomal dominant.

25,33% = 86,2%

Sadowski CE, Lovric S, Ashraf S et al.
A single-gene cause in 29.5% of cases of steroid-resistant nephrotic syndrome.
J Am Soc Nephrol 2014;26:1279–128

- **Panel restringido:**

-Deja un 15% de posibilidades de hallar una mutación relacionada al SN.

- **Panel ampliado:**

-Si se halla alguna mutación = Diagnostico.

-No halla mutación= completar con WES (whole exomic sequencing).

¿PODEMOS DIFERENCIAR LOS SNCR PRIMARIOS INMUNOLOGICOS DE LOS GENETICOS?

TABLE 1 | Urine and serum based biomarkers and their correlation to nephrotic syndrome subtypes.

Biomarker	Disease state with high levels	Disease state with low levels	Healthy controls	ROC AUC
CD80 (22)	MCD- active	FSGS- remission MCD	Present at low levels	0.925
NGAL (20)	SRNS	SSNS	Present at low levels	0.91
uVDBP	SRNS	SSNS	Present at very low levels	0.87
A1BG (21)	Full size and truncated protein—SRNS	Full size protein—SSNS	Absent	
suPAR (51)	FSGS	MCD	Present at low levels	
Hemopexin (46)	MCD- remission	MCD- relapse	Present at high levels	
CLCF-1 (61)	FSGS- recurrence	FSGS	Present at low levels	
CD40 (65)	FSGS- recurrence	FSGS	Present at low levels	
Angptl4 (64)	Heavy proteinuria, regardless of underlying cause	Remission states with low to no proteinuria	Present at low levels	

frontiers in Pediatrics

REVIEW
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The Search for Biomarkers to Aid in Diagnosis, Differentiation, and Prognosis of Childhood Idiopathic Nephrotic Syndrome

*Hillarey Stone [1], Bliss Magella [1] and Michael R. Bennett [1,2]**

¿ES POSIBLE DIFERENCIAR EN LA ANATOMIA PATOLOGICA EL ORIGEN DE LA EFS?

Table 1. Causes of FSGS

Primary	Circulating podocyte-toxic factor
Secondary: Maladaptive	Reduced number of functioning nephrons (*e.g.*, unilateral renal agenesis, renal dysplasia, oligomeganephronia, glycogen storage disease, low birth weight)
	Abnormal stress on an initially normal nephron population (*e.g.*, morbid obesity, surgical reduction of renal mass [usually >75%], reflux nephropathy, high-protein diet, sickle cell disease, any advanced kidney disease with substantial loss of nephrons)
	Other causes: sleep apnea, cyanotic congenital heart disease, renal artery stenosis, malignant hypertension, cholesterol emboli
Secondary: Viral	HIV (established), CMV (probably), parvovirus B19 (possibly), EBV (possibly), HCV (possibly), hemophagocytic syndrome (possibly)
Secondary: Drug induced	Direct-acting antiviral therapy (ledipasvir, sofosbuvir), mTOR inhibitors, calcineurin inhibitors, anthracyclines, heroin(adulterants), lithium, IFN, anabolic steroids
Genetic	Renal limited (Table 2)
	Syndromic (Table 3)
Unknown	

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, Hepatitis C virus; mTOR, mammalian target of rapamycin. IFN, interferon

Differentiating Primary, Genetic, and Secondary FSGS in Adults: A Clinicopathologic Approach

An S. De Vriese,[1] Sanjeev Sethi,[2] Karl A. Nath,[3] Richard J. Glassock,[4] and Fernando C. Fervenza[3]

J Am Soc Nephrol 29: ●●●–●●●, 2018. doi: https://doi.org/10.1681/ASN.2017090958

Table 4. Differential diagnostic characteristics of primary FSGS, genetic FSGS, maladaptive FSGS, and FGGS

	Primary FSGS	Genetic FSGS	Maladaptive FSGS	FGGS
Clinical	NS	NS common in childhood, less common in adults	Nephrotic- or subnephrotic-range proteinuria without NS	Variable proteinuria, usually subnephrotic
LM	FSGS Often no other damage (unless late in disease course) Glomerulomegaly uncommon	FSGS FGGS common in adult-onset, uncommon in juvenile forms	FSGS Often perihilar Other signs of scarring FGGS in many glomeruli Glomerulomegaly common	FGGS No FSGS No glomerulomegaly Ischemic glomeruli[a] Associated with tubulointerstitial fibrosis, vascular sclerosis
EM	Diffuse FPE (>80%)	Variable (diffuse or segmental) FPE, characteristic features in some mutations	Segmental FPE	Minimal or no FPE in unaffected glomeruli

NS, nephrotic syndrome.

[a]Characterized by thickening and wrinkling of the GBM and distention of the Bowman space.

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DIAGNOSTICAR Y TRATAR…

¿A QUIEN?....

Table 2. Genetic causes of FSGS: Renal-limited FSGS

Gene Locus Inheritance	Protein	Protein Function	Phenotype	Response to Therapy
Slit diaphragm–associated proteins				
NPHS1 19q13.1 AR	Nephrin	Essential component of the slit diaphragm	Finnish type congenital nephrotic syndrome, sporadic childhood FSGS, rarely adult-onset FSGS	Resistant to immunosuppression, reported patients with response to immunosuppression in heterozygous mutations or variants
NPHS2 1q25.2 AR	Podocin	Transmembrane protein involved in recruitment of nephrin to the slit diaphragm	Familial or sporadic FSGS or DMS in early childhood–, adolescence- or adult-onset FSGS in particular in compound heterozygotes for one pathogenic NPHS2 mutation and p.R229Q polymorphism	Resistant to immunosuppression, reported patients with response to immunosuppression in heterozygous mutations or variants
CD2AP 6p12 AD, rarely AR	CD2-associated protein	Scaffolding molecule between slit diaphragm and actin cytoskeleton	Childhood-onset FSGS	Resistant to immunosuppression
PLCE1 10q23.33 AR	Phospholipase Cε1	Signaling protein, interacts with nephrin	Isolated DMS, sporadic and familial early childhood–onset FSGS	Reported patients with (partial) response to immunosuppression
TRPC6 11q22.1 AD	Transient receptor potential cation channel 6	Receptor-activated calcium channel localized at the foot process membrane, interacts with nephrin and podocin	Familial or sporadic adult-onset FSGS, childhood-onset FSGS has also been described	Reported patients with (partial) response to cyclosporin
MAGI2 7q11.23-q21.11 AR	Membrane-Associated Guanylate Kinase, WW, and PDZ domain–containing 2	Scaffolding molecule between slit diaphragm and actin cytoskeleton	Familial and sporadic congenital nephrotic syndrome	Resistant to immunosuppression
Actin cytoskeleton and regulation				
ACTN4 19q13 AD	α–Actinin-4	Member of the spectrin gene superfamily, cytoskeletal protein	Familial or sporadic adult-onset FSGS	Resistant to immunosuppression
MYO1E 15q22.2 AR	Nonmuscle myosin 1e	Involved in intracellular movement and membrane trafficking	Familial childhood-onset FSGS	Reported patients with (partial) response to cyclosporin
ANLN 7p15-p14 AD	Anillin	F-actin binding protein, involved in slit diaphragm-cytoskeleton binding	Familial adult-onset FSGS	Resistant to immunosuppression
ARHGDIA 17q25.3 AR	Rho GDP dissociation inhibitor α	Regulation of podocyte migratory phenotype and shape	Congenital or early childhood-onset nephrotic syndrome	Resistant to immunosuppression, may respond to RAC1 inhibitors (eplerenone)
ARHGAP24 4q22.1 AD	RhoGTPase activating protein 24	Regulation of podocyte migratory phenotype and shape	Adolescence-onset FSGS	Resistant to immunosuppression
TTC21B 2q24.3 AR	Tetratricopeptide repeat domain 21B	Intraflagellar transport-A component, regulation cytoskeleton adult podocytes	Adolescence- or adult-onset FSGS associated with atrophic tubules	Resistant to immunosuppression
KANK2 19p13.2 AR	Kidney ankyrin repeat-containing protein 2	Regulation Rho GTPase activity in podocytes (cell migration and shape)	Familial early-onset SRNS	Resistant to immunosuppression

Gene Locus Inheritance	Protein	Protein Function	Phenotype	Response to Therapy
Nuclear pore complex proteins				
NUP93 16q13 AR	Nucleoporine 93 kD	Component of the nuclear pore complex	Familial childhood-onset SRNS	Resistant to immunosuppression
NUP205 7q33 AR	Nucleoporine 205 kD	Component of the nuclear pore complex	Familial childhood-onset SRNS	Resistant to immunosuppression
XPO5 6p21.1 AR	Exportin 5	Component of the nuclear pore complex	Familial childhood-onset SRNS	Resistant to immunosuppression
NUP107 12q15 AR	Nucleoporine 107 kD	Component of the nuclear pore complex	Childhood-onset FSGS	Resistant to immunosuppression
Cell membrane–associated proteins				
PTPRO 12p13-p12 AR	Protein tyrosine phosphatase, receptor type O	Member of the R3 subtype family of protein tyrosine phosphatases at the apical surface of polarized cells	Childhood-onset FSGS	Resistant to immunosuppression, reported patients with partial response to immunosuppression
EMP2 16p13.2 AR	Epithelial membrane protein 2	Regulation of the amount of CAVEOLIN-1, EMP2 depletion causes decreased cell proliferation	Childhood-onset FSGS	Reported patients with response to steroids
PODXL 7q32.3 AD	Podocalyxin	Component of glycocalyx	Familial childhood- and adult-onset FSGS	Resistant to immunosuppression
GBM protein				
LAMA5 20q13.2-q13.3 AD (?)	Laminin α-5	Member of the α-subfamily of laminin chains, major component of basement membranes	Adult-onset FSGS	Likely resistant to immunosuppression

AR, autosomal recessive; DMS, diffuse mesangial sclerosis; AD, autosomal dominant; SRNS, steroid-resistant nephrotic syndrome.

¿NO HABRÍA QUE TRATAR A NINGUN SNCR GENETICO?

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Pediatr Nephrol. 2019 November ; 34(11): 2279–2293. doi:10.1007/s00467-018-4093-1.

Treatment of steroid-resistant nephrotic syndrome in the genomic era

Adam R. Bensimhon[1], Anna E. Williams[1], Rasheed A. Gbadegesin[1,2,3]

[1]Department of Pediatrics, Division of Nephrology, Duke University Medical Center, Durham, NC 27710, USA

¿Como identificar ese «subset» de SNCR que responderían?

- ✓ Confrontar la mutación y respuesta a tratamiento con la literatura actualizada (Clinvar), en caso de resultado ambiguo o nulo, trial terapéutico con CSA o TRACO.

suggests that testing should be guided by the genetic architecture of the disease in the population. Notably, most genetic forms of SRNS do not respond to current immune-suppressive therapies; however, a small subset of patients with monogenic SRNS will achieve partial or complete remission with specific immunomodulatory agents, presumably due to non-immunosuppressive effects of these agents. We suggest a pragmatic approach to the therapy of genetic SRNS, as there is no evidence-based algorithm for the management of the disease.

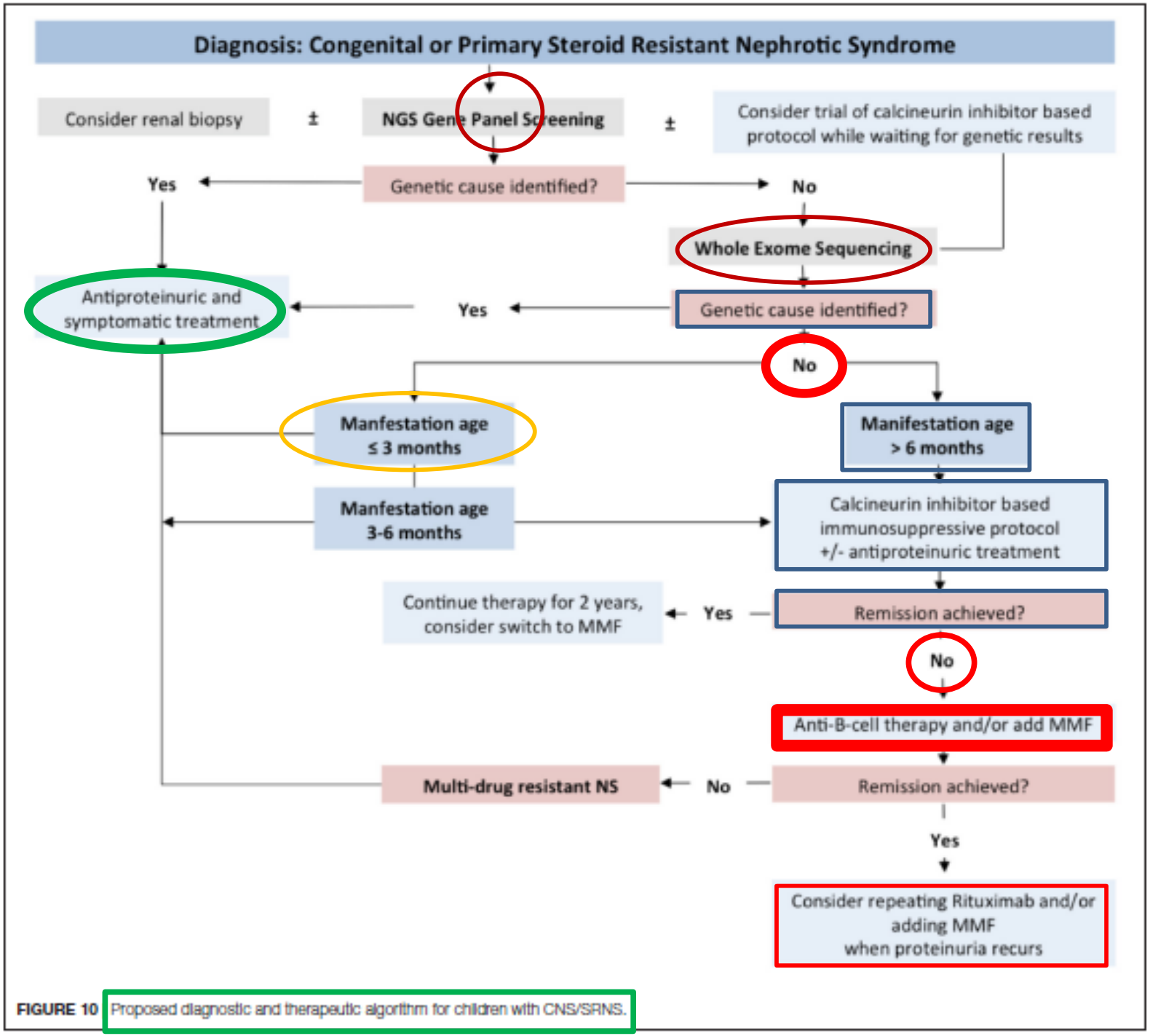

FIGURE 10 Proposed diagnostic and therapeutic algorithm for children with CNS/SRNS.

Citation:
Trautmann A, Lipska-Ziętkiewicz BS and Schaefer F (2018) Exploring the Clinical and Genetic Spectrum of Steroid Resistant Nephrotic Syndrome: The PodoNet Registry. Front. Pediatr. 6:200. doi: 10.3389/fped.2018.00200

CONDUCTA Y EVOLUCION

➢ Paciente 1

-Conducta:

- ✓ **Solicite que la OS amplíe estudio, no se acepta.**
- ✓ **Con «estudio Genetico» negativo, asumo SNCR INMUNOLOGICO**
- ✓ **Inicio tratamiento con CICLOSPORINA**
- ✓ **Respuesta: negativiza proteinuria dentro de las 2 semana, y hasta la actualidad con 1 año de tto. no presenta recaídas.**

➢ Paciente 2

-Conducta:

- ✓ **Con «estudio Genetico» positivo, siendo una VUS que afecta una proteína que estabilizarían los inhibidores de la calcineurina.**
- ✓ **Inicio tratamiento con CICLOSPORINA.**
- ✓ **Respuesta: descenso progresivo de proteinuria.**
- ✓ **Ultimo laboratorio (11/3/22): 1 año de tto, Ind Proto/Cr: 0,22 – IndAlbo/ Cro: 74,6 mg/gr – Crp 0,41 – Up 36)**

MUCHAS GRACIAS!...